



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region **PH&T@LH0**

Telephone (973) 526-6004

July 1, 1999

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

WARNING LETTER

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

Wayne Yetter, President & CEO
Novartis Pharmaceuticals Inc.
59 Route 10
East Hanover, New Jersey 07936

FILE NO.: 99-NWJ-29

Dear Mr. Yetter:

During an inspection of your facility located at 556 Morris Avenue, Summit, New Jersey, by the U.S. Food and Drug Administration, between the dates of April 20 and May 7, 1999, our investigators documented serious deviations from the current Good Manufacturing Practices Regulations (Title 21, Code of Federal Regulations, Part 210 and 211) in conjunction with your firm's manufacture of prescription drug products.

These deviations were presented to your firm's attention on a FDA-483, List of Observations, at the close of the inspection on May 7, 1999. These cGMP deficiencies cause your products to be adulterated within meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

The significant observations are as follows:

1. The firm does not have sufficient data to adequately support the expiration date extension from two years to three years for the product Tegretol XR 100mg tablets. Tegretol XR Lot #B010302, manufactured August 1992, was designated as a stability batch and the data generated from this lot was used to extend the product expiration from two years to three years. Lot #B010302 was only tested on stability for two years. The stability study was terminated after only two years.

Additionally, Lot #B010302 was drilled using a [REDACTED] although the only approved method in the application for drilling is using a [REDACTED]. Therefore, this lot should not be used as a stability extension lot.

Novartis Pharmaceuticals, Inc.
Warning Letter #99-NWJ-29
July 1, 1999

2. Lack of assurance that the products Tegretol XR 100mg, 200mg, and 400mg tablets will meet all specifications at the end of expiry. The firm does not have sufficient data to support the two year expiration date for bottles and no assurance that the tablets packaged in blister packs will meet all specifications at the end of expiry.

The firm failed to place the following Tegretol XR marketed packaged dosage forms into their annual stability program as required by your Standard Operating Procedure (SOP) #VT-005-02 Stability Testing Program for Marketed Products.

- 1996-Tegretol XR 100mg tablets-Bottles of 100's
 - Hospital Unit (acler blister pack)
- Tegretol XR 200mg tablets-Hospital Unit (acler blister pack)
- Tegretol XR 400mg tablets-Hospital Unit (acler blister pack)
- 1997-Tegretol XR 100mg tablets-Hospital Unit (acler blister pack)
 - Sample size bottle of 6's
- Tegretol XR 200mg tablets-Hospital Unit (acler blister pack)
 - Sample size bottle of 4's
- Tegretol XR 400mg tablets-Bottles of 100's
 - Sample size bottle of 4's
 - Sample size bottle of 6's
- 1998-Tegretol XR 100mg tablets-Hospital Unit Dose
- Tegretol XR 200mg tablets-Hospital Unit Dose

3. The firm failed to store the Tegretol XR tablet lots on stability in their marketed containers throughout the shelf life of the product. There is no assurance that the tablets, which are in their marketed containers, will meet all specifications. For Example:

- a. The 1997 annual stability lot for Tegretol XR 100mg tablets, lot #1B224388, manufactured March 1997 and expired March 1999, was packaged on January 21, 1998, 10 months after the date of manufacture. The firm did not test this lot at the required 12-month time interval. The stability study for lot #1B224388 was terminated at the 14-month stability station.

Novartis Pharmaceuticals, Inc.
Warning Letter #99-NWJ-29
July 1, 1999

This product has a 24-month expiration date. Stability testing was not conducted on product packaged in the marketed container and stored at a controlled room temperature (██████████) throughout the expiration date.

- b. The 1998 annual stability lot for Tegretol XR 100mg tablets, lot # 488006R2, manufactured June 1998 and expires June 2001, was packaged on February 4, 1999, 8 months after manufacturing. No testing was performed at the 6-month interval for this lot. The stability matrix shows testing requirements for this lot are 12-month, 24-month, and 28-month intervals. This lot will be stored in the marketed container at ██████████ RH for 28-months and the product has a 36-month expiration date.
- 4. The firm does not have sufficient data to support the analytical method transfer from their facility in Summit, New Jersey to their facility in East Hanover, New Jersey. The firm's Method Transfer Protocol, which was prepared to transfer the analytical testing methods, did not require testing of the Tegretol XR 100mg and 400mg tablets, and only required testing of one lot of the 200mg tablets.

The Method Transfer Report for Tegretol XR 200mg tablets revealed the assay acceptance criteria was changed, after it was discovered that the individual assay results generated at the Summit facility, were lost. The firm did not conduct an investigation into the lost data. The Method Transfer Report for the Tegretol XR 200mg tablets was approved, although the data was lost and the firm changed the assay acceptance criteria. The Method Transfer Protocol and the Method Transfer Report were not signed nor dated.

- 5. The firm's current system for preparing the Annual Product Reviews is inadequate in that numerous omissions and incorrect data were contained in the Tegretol XR Annual Product Reviews for 1996, 1997, and 1998. For Example:
 - a. The 1996, 1997, and 1998 Annual Product Reviews for Tegretol XR tablets states the validation commitment batches are part of the stability program. The firm never placed those batches in the stability program.

Novartis Pharmaceuticals, Inc.
Warning Letter #99-NWJ-29
July 1, 1999

- b. The annual product reviews did not include all stability results. A problem in the firm's computer system prevented the results of stability data from printing. Additionally, the stability data from these annual reviews was used to support the Tegretol XR expiration date extension.
- c. The 1997 Annual Product Review for Tegretol XR 400mg tablets did not include four batches (#B227189, #B227190, #B227191, & #B227192) which were rejected for failure to meet release rate specification.
- d. The 1996 or 1997 Annual Product Review did not include Tegretol XR 200mg batches (#B012857, #B177977, #B012950, & #B012952) that were manufactured in 1996.

Additionally, during the inspection there were questions raised by the Investigator concerning your validation of the product Tegretol XR 400mg tablets, from the time of the product's approval in March 1996 through November 1997. There were numerous product batch failures from 1996 through 1997. The Agency acknowledges that the firm has addressed those validation concerns, prior to our inspection.

We have received your written response dated May 21, 1999, regarding the inspectional observations noted on the FDA-483. We will evaluate the implementation and the adequacy of your proposed corrective actions during the follow-up inspection of your firm.

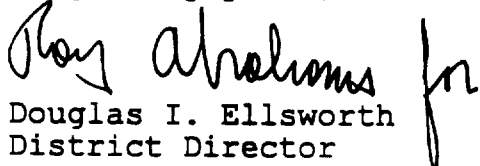
The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practices Regulations. We request that you take prompt action to correct any noted violations not already corrected and undertake a comprehensive evaluation of your cGMP compliance. Failure to promptly correct these violations may result in regulatory action without further notice. This includes seizure and/or injunction.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, pending new drug applications (NDA's) or export approval requests may not be approved until the aforementioned violations are corrected.

Novartis Pharmaceuticals, Inc.
Warning Letter #99-NWJ-29
July 1, 1999

Any additional information you wish to submit should be sent to the U.S. Food and Drug Administration, New Jersey District Office, 10 Waterview Blvd, 3rd Floor, Parsippany, New Jersey, 07054, Attention: Andrew Ciaccia, Compliance Officer.

Very truly yours,

A handwritten signature in cursive script, appearing to read "Doug Ellsworth for".

Douglas I. Ellsworth
District Director
New Jersey District Office

AC:slm